#11 Cont

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

97. (Amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a retroviral promoter is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding sequences.

#12

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - vi).

REMARKS

Claim amendments

Claims 1, 17, 28, 56, 66 and 74 have been amended to indicate that the heterologous promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector. Support for the amendments can be found, for example, on page 10, lines 13-16 of the specification. The claims have also been amended to more clearly indicate that the heterologous promoter regulates expression of a coding sequence after infection of a target cell.

3. Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 under 35 U.S.C. §112, first paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention" (Office Action, page 3). The Examiner states that Applicants "have failed to note support" for the following added claim language: a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based (Office Action, pages 3-4). The Examiner states that "[w]hile the specification provides an example of insertion of promoters from a cellular gene, it does not provide support for the claimed genus of retroviral promoters" (Office Action, page 4).

Applicants respectfully disagree. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111,1116 (Fed. Cir. 1991)). As noted in the Manual of Patent Examining Procedure (MPEP):

> [t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . ., reduction to drawings . . . , or by disclosure of relevant, identifying characteristics, i.e., structure or other physical or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (MPEP 8th ed., revised February 2003, §2163, page 2100-168).

As also noted in the MPEP, "there may be situations where one species adequately supports a genus" (MPEP 8th ed., revised February 2003, §2163, page 2100-168).

Applicants claim a retroviral vector which undergoes promoter conversion comprising a 5' long terminal repeat region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing *a heterologous promoter (e.g., a retroviral promoter)* other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, *said promoter regulating, after infection of a target cell, expression of said one or more*

sequences selected from coding and non-coding sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.

In the specification as filed, Applicants insert the mouse mammary tumor virus (MMTV) promoter into a murine leukemia virus (MLV) retroviral vector (*i.e.* BAG) (specification, Example 1). The MMTV promoter is a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based (*i.e.*, the MLV BAG vector). In addition, Applicants show that the MMTV promoter functioned in the BAG vector as claimed. That is, Applicants showed that the β-gal gene, which is in the body of the BAG retroviral vector, was under transcriptional control of the heterologous MMTV promoter after infection *in vitro* and *in vivo* (specification, Example 1, page 21, line 1 - page 24, line 2). One skilled in the art is aware of many "retroviral vectors" as well as "heterologous promoters" (*e.g.,* retroviral promoter) which are not the promoter of the retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based (*e.g.,* specification, page 6, lines 3-16; page 11, line 26 - page 12, line 17). One of skill in the art is also well aware of methods of cloning such a "heterologous promoter" into a "retroviral vector" and assessing whether the "heterologous promoter regulates, after infection of a target cell, expression of one or more sequences selected from coding and non-coding sequences" in the body of the retroviral vector. Applicants have demonstrated these methods in the specification as filed. Furthermore, methods of assessing whether the heterologous promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector are also routine to one of skill in the art.

Clearly, based on the scope of the disclosure, the nature of the invention, the identifying characteristics disclosed, and the level of skill in the art, a person of skill in the art would recognize that Applicants were in possession of a retroviral vector which undergoes promoter conversion comprising a 5' long terminal repeat region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing *a heterologous promoter (e.g., a retroviral promoter)* other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral

vector is based is inserted, *said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.*

6. Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 under 35 U.S.C. §112, second paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32 and 56-78 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 4). The Examiner states that the claims "are indefinite for recitation of the phrase 'a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based' because the metes and bounds of the claimed promoter are unclear" (Office Action, page 4).

Applicants respectfully disagree. The test for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification" (*Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986)).

As amended, the claimed invention relates to a retroviral vector which undergoes promoter conversion comprising a 5' long terminal repeat region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing *a heterologous promoter (e.g., a retroviral promoter)* other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, *said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.* The language clearly indicates to a person of skill in the art (*e.g.*, Couture *et al.*) that the heterologous promoter does not naturally occur in the retroviral vector and is not related to the retroviral vector. Furthermore, as pointed out above, one of skill in the art can

determine whether the promoter regulates, after infection of a target cell, expression of the one or more sequences selected from coding and whether the promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector, using routine skills.

9. Rejection of Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72 and 74-78 under 35 U.S.C. §103(a)

Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72 and 74-78 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al." (Office Action, page 5). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector" (Office Action, page 6).

Applicants respectfully disagree. Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.*

There is no particular teaching in the art cited directing the skilled person to insert into a partially deleted U3 region of a retroviral vector, *a heterologous promoter (e.g., a retroviral promoter) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based,* in order to obtain expression of a coding sequence in the body of the retroviral vector. As pointed out below, the data in Couture *et al.* would clearly discourage a person of skill in the art from doing so, and Faustinella *et al.* do not teach or even suggest that the promoter in the 3' U3 region of the MLV can be replaced with a heterologous promoter which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based, for the purpose of directing expression of a coding sequence in the body of the vector (*i.e.,* directing the expression of a coding sequence which is not directly linked to the heterologous promoter in the retroviral

vector). Indeed, as the Examiner notes, "Faustinella et al. is ***only cited for*** its teaching of a polylinker in the U3 region as a convenient structure to insert a desired sequence by recombinant DNA techniques" (Office Action, page 13, emphasis added).

As amended, the claimed invention relates to a retroviral vector which undergoes promoter conversion comprising a 5' long terminal repeat region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing *a heterologous promoter (e.g., a retroviral promoter)* other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, *said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector*. Applicants teach in the specification as filed that in the claimed retrovial vectors,

> both LTRs will consist to a large extent of heterologous promoter/enhancer sequences in the target cell. This will reduce the likelihood of the integrated vector in the target cell being subject to the same inactivation over long periods as has been described for conventional vectors (Xu *et al., Virology, 171*:331-334 (1989)) and also will reduce the chance of recombination with endogenous retroviral sequences to generate potentially pathogenic replication competent virus, increasing the safety of the system (specification, page 10, lines 6-16).

Couture *et al.* teach that the homology between the U3 region of MoMLV and the U3 regions from the five related murine retroviruses (*i.e.*, SL3-3, AKV, Xeno, HaMSV and MPSV) range between 98% (HaMSV, MPSV) and 64% (Xeno). However, Couture *et al.* teach that "several noticeably conserved regions exist" (Couture *et al.*, page 669, column 2). The presence of conserved regions in the U3 regions of the five related murine retroviruses, increases the chance of the chimeric LTR recombining with endogenous retroviral sequences to generate potentially pathogenic replication competent virus.

Furthermore, as indicated in the data compiled in Table 2 of Couture *et al.*, generally the lower the degree of homology between the sequences, the lower the yield of the chimeric LTR

(chLTR) vector. For example, compare the titers of the Xeno chLTR (64% homology) with the titers of the HaMSV chLTR (98% homology). Couture *et al.* teach that "Xeno [64% homology] and AKV [76% homology] chLTRs would ***not be useful*** in the cell types tested ***unless low levels of gene expression are sought***" (Couture *et al.*, page 675, column 2, emphasis added). Although the SL-3 construct produced "a nearly two-fold increase in activity over MoMLV" in JURKAT cells, the SL-3 construct was also "the only construct that yielded lower levels of activity than Moloney" (Couture *et al.*, page 669, column 2 - page 672, column 1). The results of Couture *et al.* show that although murine LTRs that are "related" to (Couture *et al.*, abstract) and have "minimally substituted U3 regions" with (Couture *et al.*, page 675) the MoMLV U3 region, those with lower homology generate lower levels of gene expression.

Clearly, the results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector *a heterologous promoter (e.g., a retroviral promoter) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based* in order to obtain expression of a coding sequence in the body of the retroviral vector.

Faustinella *et al.* do not provide what is lacking in the Couture *et al.* reference to render obvious Applicants' claimed invention. Faustinella *et al.* teach a modified MLV vector comprising a partially deleted 3' U3 region which is substituted by either a luciferase reporter gene directly linked to a rous sarcoma virus promoter or a hygromycin resistance gene directly linked to a herpes simplex thymidine kinase promoter. Alternatively, Faustinella *et al.* teach that the gene directly linked to the promoter can be subcloned into the body of the vector. Faustinella *et al.* do not teach or even suggest that the promoter in the 3' U3 region of the MLV can be replaced with a heterologous promoter which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based, for the purpose of directing expression of a coding sequence in the body of the vector (*i.e.*, directing the expression of a coding sequence which is not directly linked to the heterologous promoter in the retroviral vector).

There is no particular teaching in the art cited directing the skilled person to insert into a partially deleted U3 region of a retroviral vector *a heterologous promoter (e.g., a retroviral promoter) other than a promoter from a retrovirus upon which the retroviral vector is based or a*

promoter from a subtype of the retrovirus upon which the retroviral vector is based in order to obtain expression of a coding sequence in the body of the retroviral vector.

The prior art combination of record has been made with the advantage of impermissible hindsight, and thus, the rejection is legally improper. That is, the Examiner has ***not*** taken into account "***only*** knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made" and has included "knowledge gleaned ***only*** from applicant's disclosure" (*In re McLaughlin*, 170 U.S.P.Q. 209, 212, (CCPA 1971), emphasis added). In making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of the desirability of inserting into a partially deleted U3 region of a retroviral vector *a heterologous promoter (e.g., a retroviral promoter) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based* in order to obtain expression of a coding sequence in the body of the retroviral vector. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicants' disclosure for the suggestion that the cited references should be combined and the expectation of success (*In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531-1532 (Fed. Cir. 1988)). In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention.

10. Rejection of Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72 and 74-78 under 35 U.S.C. §103(a)

Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72 and 74-78 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. . . . and further in view of Mee et al." (Office Action, page 7). The Examiner states that Couture *et al.* in view of Faustinella *et* al. do not show MMTV promoters or regulatory elements (Office Action, page 7). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied . . . . above by insertion of an

MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types" (Office Action, page 7).

As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Mee *et al.* do not provide the teaching lacking in the Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Mee *et al.* disabled the 3' LTR of a retroviral vector and cloned the HRE inducible promoter of the MMTV and the *aph* gene directly between the LTRs of the provirus, *i.e.,* into the body of the vector, producing a *self-inactivating (SIN) retroviral vector* (Mee *et al.*, pages 289-290). In contrast, Applicants teach a *non-SIN retroviral vector*. Mee *et al.* do not teach insertion of a heterologous promoter into a partially deleted U3 region of a retroviral vector.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.* and Mee *et al.* do not render obvious Applicants' claimed invention.

11. Rejection of Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95 and 97-101 under 35 U.S.C. §103(a)

Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95 and 97-101 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. . . . and further in view of Mehigh et al." (Office Action, page 7). The Examiner states that Couture *et al.* in view of Faustinella *et al.* do not show "cellular promoters or regulatory elements" (Office Action, page 8). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied . . . . above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle" (Office Action, page 8).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Couture *et al.* teach that chLTRs from related and minimally substituted murine retroviruses (*e.g.,* Xeno [64% homology] and AKV [76% homology] chLTRs "would ***not be useful*** in the

cell types tested ***unless low levels of gene expression are sought***" (Couture *et al.*, page 675, column 2, emphasis added). Clearly, the results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector a heterologous promoter (e.g., a retroviral promoter or ***a promoter from a cellular gene (Claim 33)***) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based in order to obtain expression of a coding sequence in the body of the retroviral vector.

Mehigh *et al.* do not provide the teaching lacking in the Couture *et al.* and Faustinella *et al.* references. Mehigh *et al.* fused the Whey acidic protein promoter (WAP) or the mouse mammary tumor virus (MMTV) promoter to the gene encoding synthetic bovine growth hormone-releasing factor (bGRF). Mehigh *et al.* teach that the plasmids "were able to induce transcription of bGRF upon transfection into . . . bovine kidney cells and induction with a lactogenic hormonal milieu . . . or dexamethasone" (Mehigh *et al.*, abstract). Mehigh *et al.* further teach that when the "constructs were cloned into a BLV vector in place of its oncogenic region, and transfected into MDBK cells, bGRF was expressed" (Mehigh *et al.*, abstract). Mehigh *et al.* do not teach insertion of a heterologous promoter into a partially deleted U3 region of a retroviral vector.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.* and Mehigh *et al.* do not render obvious Applicants' claimed invention.

12. Rejection of Claims 1, 13, 14, 33, 40, 41, 56, 63, 64, 79, 86 and 87 under 35 U.S.C. §103(a)

Claims 1, 13, 14, 33, 40, 41, 56, 63, 64, 79, 86 and 87 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.*; and further as evidenced by Miller *et al.* and Panganiban *et al.* (Office Action, pages 7-8). The Examiner concludes that "the vectors of claims 13 and 14 are taught by the above cited combinations of references as evidenced by Miller et al. and Panganiban et al." (Office Action, page 9).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further

in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention. Couture *et al.* teach that chLTRs from related and minimally substituted murine retroviruses (*e.g.*, Xeno [64% homology] and AKV [76% homology] chLTRs "would ***not be useful*** in the cell types tested ***unless low levels of gene expression are sought***" (Couture *et al.*, page 675, column 2, emphasis added). Clearly, the results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector a heterologous promoter (e.g., a retroviral promoter, ***a promoter from a cellular gene (Claim 33) or a non-retroviral promoter (Claim 79)***) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based in order to obtain expression of a coding sequence in the body of the retroviral vector.

The teachings of Miller *et al.* and Panganiban *et al.* do not provide the teaching that is lacking. As discussed in the previously filed amendments, Miller *et al.* designed "a set of retroviral vectors which facilitate cDNA transfer and expression" (Miller *et al.*, page 986, column 3), one of which is the LXSN retroviral vector used by Couture *et al.* to generate their vectors. Panganiban *et al.* ('84) mutagenized cloned spleen necrosis virus and showed that the 3' end of the *pol* gene of the spleen necrosis virus encodes a polypeptide required for DNA integration through interaction with the *att* site. Neither Miller *et al.* nor Panganiban *et al.* teach or even suggest a retroviral vector wherein the U3 region comprises a heterologous promoter *which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based* and which regulates expression of a coding sequence inserted into the body of the vector after infection of the target cell.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further as evidenced by Miller *et al.* and Panganiban *et al.* do not render obvious Applicants' claimed invention.

13. Rejection of Claims 1, 10, 33, 37, 56, 60, 79, 83, 89 and 96 under 35 U.S.C. §103(a)

Claims 1, 10, 33, 37, 56, 60, 79, 83, 89 and 96 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of

Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.*; and further in view of Price *et al.* (Office Action, pages 9-10). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of the above cited combinations of references by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector" (Office Action, page 10).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; and Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention. Couture *et al.* teach that chLTRs from related and minimally substituted murine retroviruses (*e.g.*, Xeno [64% homology] and AKV [76% homology] chLTRs "would ***not be useful*** in the cell types tested ***unless low levels of gene expression are sought***" (Couture *et al.*, page 675, column 2, emphasis added). Clearly, the results of Couture *et al.* do not motivate a person of skill in the art to insert into a partially deleted U3 region of a retroviral vector a heterologous promoter (e.g., a retroviral promoter, ***a promoter from a cellular gene (Claim 33) or a non-retroviral promoter (Claim 79)***) other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based in order to obtain expression of a coding sequence in the body of the retroviral vector.

The teaching of Price *et al.* does not provide the teaching that is lacking. As discussed in the previously filed amendments, Price *et al.* inserted the β-gal gene, the SV40 early promoter and the Tn5 *neo* gene into the body of the pDOL vector, which is derived from the Moloney murine leukemia virus (Mo-MuLV), and used the vector as a cell-lineage marking system applicable to the vertebrate nervous system. There is clearly no discussion in the Price *et al.* reference regarding the manipulation of the U3 region of the pDOL vector for any purpose.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further in view of Price *et al.* do not render obvious Applicants' claimed invention.

14. Rejection of Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, 76, 89, 96, 97, 98 and 99 under 35 U.S.C. §103(a)

Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, 76, 89, 96, 97, 98 and 99 are rejected under 35 U.S.C. §103(a) as being unpatentable over Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture et al. in view of Faustinella et al. and further in view of Mehigh *et al.*; and further in view of Longmore *et al.* and Kay *et al.* (Office Action, pages 10-11). It is the Examiner's opinion that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the combinations of references cited above to express a therapeutic protein because Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal" (Office Action, page 11).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; and Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* do not render obvious Applicants' claimed invention.

The teachings of Longmore *et al.* and Kay *et al.* do not provide the teaching that is lacking. As discussed in the previously filed amendments, Longmore *et al.* infected mice with a recombinant spleen focus-forming retrovirus (SFFV) expressing an oncogenic erythropoietin (Epo) receptor (EpoR) and showed a relationship between erythropoiesis and thrombopoiesis at the level of the Epo-EpoR signalling pathway. In addition, Longmore *et al.* teach that the SFV-based vectors "may be excellent vehicles for the introduction of genes into multipotent, hematopoietic progenitors, in vitro" (Longmore *et al.*, abstract). Using an amphotropic retroviral vector that encoded the canine factor IX complementary DNA, Kay *et al.* determined that a method for hepatic gene transfer *in vivo* by the direct infusion of recombinant retroviral vectors into the portal vasculature of a hemophilia B dog model, which results in the persistent expression of exogenous genes, may be feasible for the treatment of hemophilia B patients. There is no discussion in the Longmore *et al.* or Kay *et al.* references regarding the manipulation of the U3 region of their retroviral vectors for any purpose.

Clearly, the combined teachings of Couture *et al.* in view of Faustinella *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mee *et al.*; Couture *et al.* in view of Faustinella *et al.* and further in view of Mehigh *et al.* and further in view of Longmore *et al.* and Kay *et al.* do not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Four times amended) A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

d) a 5' long terminal repeat region of the structure U3-R-U5;

e) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and

f) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.

17. (Four times amended) A retroviral vector kit comprising:
a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter is inserted, wherein said promoter is derived from a promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based and said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and

non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector; and

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

28. (Four times amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter is inserted, wherein said promoter is other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based and said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.

33. (Amended) A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

a) a 5' long terminal repeat region of the structure U3-R-U5;

b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and

c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a promoter from a cellular gene is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences.

43. (Amended) A retroviral vector kit comprising:

a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a promoter from a cellular gene is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences; and

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

51. (Amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a promoter from a cellular gene is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences.

56. (Amended) A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

a) a 5' long terminal repeat region of the structure U3-R-U5;

b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and

c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous retroviral promoter which is derived from a promoter of a retrovirus other than a retrovirus upon which the retroviral vector is based or other than a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.

66. (Amended) A retroviral vector kit comprising:

a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous retroviral promoter other than a promoter from a retrovirus upon which the retroviral vector is based or other than a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector; and

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

74. (Amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long

terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous retroviral promoter other than a promoter from a retrovirus upon which the retroviral vector is based or other than a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences and wherein said promoter has a reduced chance of recombination with endogenous sequences of the retroviral vector.

79. (Amended) A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

a) a 5' long terminal repeat region of the structure U3-R-U5;

b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and

c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a retroviral promoter is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences.

89. (Amended) A retroviral vector kit comprising:

a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a retroviral promoter is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences; and

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

97. (Amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a retroviral promoter is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding [and non-coding] sequences.